Claims

We Claim:

1. An ionically cross-linked gel comprising:
a polyacid (PA);
a polyalkylene oxide (PO); and
a multivalent cation.

2. The gel of claim 1, wherein said polyacid is selected from the group consisting of a carboxypolysaccharide, polyacrylic acid, polyamino acid, polylactic acid, polyglycolic acid, polymethacrylic acid, polyterephthalic acid, polyhydroxybutyric acid, polyphosphoric acid, polystyrenesulfonic acid, and copolymers of said polyacids.

3. The gel of claim 1, wherein the polyacid is a carboxypolysaccharide selected from the group consisting of carboxymethyl cellulose (CMC), carboxyethyl cellulose, chitin, carboxymethyl chitin, hyaluronic acid, alginate, propylene glycol alginate, pectin, carboxymethyl dextran, carboxymethyl chitosan, heparin, heparin sulfate, chondroitin sulfate and polyuronic acids including polymannuronic acid, polyglucuronic acid and polyguluronic acid..

4. The gel of claim 1, wherein the polyacid is carboxymethylcellulose.

5. The gel of claim 1, wherein the polyacid is carboxymethylcellulose having a molecular weight in the range of about 10 kd to about 10,000 kd and a degree of substitution in the range of greater than about 0 to about 3.

6. The gel of claim 1, wherein said polyalkylene oxide is selected from the group consisting of polypropylene oxide, polyethylene glycol, polyethylene oxide, and PEO/PPO block copolymers.

7. The gel of claim 1, wherein said polyalkylene oxide is polyethylene oxide or polyethylene glycol having a molecular weight in the range of about 200 d to about 8000 kd.

8. The gel of claim 1, wherein said polyalkylene oxide is polyethylene glycol having a molecular weight in the range of about 200 d to about 5 kd.

9. The gel of claim 1, wherein said PA is in the range of about 10 % to about 99 % by weight, of the total solids content.

10. The gel of claim 1, wherein the PA is in the range of about 50 % by weight to about 99 % by weight, of the total solids content.

11. The gel of claim 1, wherein the PA is in the range of about 90 % by weight to about 99 % by weight, of the total solids content.

12. The gel of claim 1, wherein the PO is in the range of about 1 % by weight to about 90 % by weight, of the total solids content.

13. The gel of claim 1, wherein the PO is in the range of about 1 % by weight to about 10 % by weight, of the total solids content.

14. The gel of claim 1, wherein the PO is about 2.5 % by weight, of the total solids content.

15. The gel of claim 1, wherein the total solids content of the gel is in the range of about 1 % to about 10 %.

16. The gel of claim 1, wherein said cation is a trivalent cation.

17. The gel of claim 1, wherein said cation is selected from the group consisting of Fe^{+3}, Al^{+3}, and Cr^{+3}.

18. The gel of claim 1, wherein said cation is a divalent cation.

19. The gel of claim 1, wherein said cation is a divalent cation selected from the group consisting of Ca^{+2}, Zn^{+2}, Mg^{+2} and Mn^{+2}.

20. The gel of claim 1, wherein said cation is accompanied by an inorganic anion.

21. The gel of claim 1, wherein said cation is accompanied by an inorganic anion selected from the group consisting of Cl, PO_4^{2-}, HPO_3^{-}, CO_3^{2-}, HCO_3^{-}, SO_4^{2-} and borates.

22. The gel of claim 1, wherein said cation is accompanied by an organic anion.

23. The gel of claim 1, wherein said cation is accompanied by an organic anion selected from the group consisting of citrate, oxalate and acetate.

24. The gel of claim 1, wherein the pH of the gel is in the range of about 2.0 to about 7.5.

25. The gel of claim 1, wherein the pH of the gel is in the range of about 2.5 to about 6.0.

26. The gel of claim 1, further comprising a drug.

27. The gel of claim 1, further comprising a drug selected from the group consisting of antithrombogenic drugs, anti-inflammatory drugs, hormones, chemotactic factors, analgesics, growth factors, cytokines, osteogenic factors and anesthetics.

28. The gel of claim 1, further comprising a drug selected from the group consisting of heparin, tissue plasminogen activator, aspirin, ibuprofen, ketoprofen, proteins and peptides containing an RGD motif, and non-steroidal anti-inflammatory drugs.

29. The gel of claim 1 having a viscosity below about 500,000 centipoise.

30. A method for manufacturing an ion-associated gel, comprising the steps of:

(a) selecting a polyacid;

(b) selecting a polyalkylene oxide;

(c) forming a solution of said polyacid and said polyalkylene oxide; and

(d) adding a cation to said solution.

31. A method for manufacturing an ion-associated gel, comprising the steps of:

(a) selecting a polyacid;

(b) selecting a polyalkylene oxide;

(c) mixing said polyacid with said polyalkylene oxide to form a dry mixture of said polyacid and said polyalkylene oxide;

(d) dissolving said mixture of polyacid and polyalkylene oxide to form an aqueous solution of polyacid and polyalkylene oxide; and

(e) adding to said aqueous solution of polyacid and polyalkylene oxide an aqueous solution comprising a cation, thereby permitting the polyacid, polyalkylene oxide and the cation to form ionic bonds.

32. The method of claim 30, wherein the polyacid is selected from the group consisting of a carboxypolysaccharide, polyacrylic acids, polyamino acids, polylactic acid, polyglycolic acid, polymethacrylic acid, polyterephthalic acid, polyhydroxybutyric acid, polyphosphoric acid, polystyrenesulfonic acid, and copolymers of said polyacids.

33. The method of claim 30, wherein the polyacid is a carboxypolysaccharide selected from the group consisting of carboxymethyl cellulose (CMC), carboxyethyl cellulose,

chitin, carboxymethyl chitin, hyaluronic acid, alginate, pectin, carboxymethyl dextran, carboxymethyl chitosan, heparin, heparin sulfate, chondroitin sulfate polyuronic acids including polymannuronic acid, polyglucuronic acid and polyguluronic acid..

34. The method of claim 30, wherein said polyalkylene oxide is selected from the group consisting of polypropylene oxide, polyethylene glycol, polyethylene oxide and copolymers of said polyalkylene oxides.

35. The method of claim 30, wherein said cation is selected from the group consisting of trivalent cations and divalent cations.

36. The method of claim 30, wherein said cation is selected from the group consisting of Fe^{+3}, Al^{+3}, and Cr^{+3}, Ca^{+2}, Zn^{+2}, Mg^{+2} and Mn^{+2}.

37. The method of claim 30, further comprising adjusting the pH in the range of about 3.5 to about 7.5.

38. The method of claim 30, further comprising the step of sterilizing the gel.

39. The method of claim 30, further comprising the step of sterilizing the gel using autoclaving or exposure to ethylene oxide.

40. A method for decreasing post-surgical adhesions comprising the step of placing the composition of claim 1 in contact with a tissue that in the absence of said gel would form an adhesion with an adjacent tissue.

41. A method for decreasing post-surgical adhesions comprising the steps of:

(a) accessing a surgical site;

(b) performing a surgical procedure; and

(c) placing the composition of claim 1 in contact with a tissue that in the absence of said gel would form an adhesion with an adjacent tissue.

42. The method of claim 40, wherein said surgical procedure is selected from the group consisting of abdominal, ophthalmic, orthopedic, gastrointestinal, thoracic, cranial, cardiovascular, gynecological, urological, plastic, musculoskeletal, spinal, nerve, tendon, otorhinolaryngological and pelvic.

43. The method of claim 40, wherein said surgical procedure is selected from the group consisting of appendectomy, cholecystectomy, hernial repair, lysis of peritoneal adhesions, kidney surgery, bladder surgery, urethral surgery, prostate surgery, salingostomy, salpingolysis, ovariolysis, removal of endometriosis, surgery to treat ectopic pregnancy, myomectomy of uterus, myomectomy of fundus, hysterectomy, laminectomy, discectomy, tendon surgery, spinal fusion, joint replacement, joint repair, strabismus surgery, glaucoma filtering surgery, lacrimal drainage surgery, sinus surgery, ear surgery, bypass anastomosis, heart valve replacement, thoracotomy, synovectomy, chondroplasty, removal of loose bodies and resection of scar tissue.

44. A method for treating symptoms of joint inflammation, comprising the step of delivering to said side of joint inflammation the composition of claim 1.

45. The method of claim 44, further comprising the steps of:

(a) accessing a site of joint inflammation; and

(b) sealing said site.

46. The method of claim 44, wherein said step of accessing is carried out using an arthroscope.

47. A method for decreasing post-traumatic adhesions, comprising the step of delivering to a site of trauma the composition of claim 1.

48. The method of claim 47, further comprising, prior to the step of delivering, the step of accessing a site of trauma.

49. A method of preventing adhesion reformation, comprising the steps of:

(a) resecting said adhesion to separate the previously adherent tissues; and

(b) placing the composition of claim 1 between the previously adherent tissues.

50. A method of claim 44, further comprising, before said step of resecting, the step of accessing a site having an adhesion.

51. A method for decreasing surgical trauma caused by a surgical instrument, comprising coating said surgical instrument with the composition of claim 1 prior to using said surgical instrument.

52. A method for decreasing friction between adjacent tissues, comprising placing the composition of claim 1 between said adjacent tissues.

53. A method for coating catheters and probes comprising contacting said catheter or probe with a composition of claim 1.

54. A dried membrane comprising a composition of claim 1.

55. The ionically cross-linked gel of claim 1, wherein the residence time is increased by increasing the viscosity of said gel.

56. A method of conditioning a dried polyacid polyalkylene oxide membrane comprising the steps of:

(a) immersing said polyacid polyalkylene oxide membrane in a solution comprising a cation or a polycation; and

(b) re-drying said membrane.

57. A dried composition comprising an association complex of a carboxypolysaccharide (CPS) and a polyether (PE), which possesses at least one property selected from the group consisting of bioresorbability, bioadhesiveness, antithrombogenicity, and antiadhesion, and wherein the composition has a pH in the range of about 2.5 to about 4.5 and is hydratable by at least about 100%.

58. The composition of claim 57, wherein the CPS is selected from the group consisting of carboxymethyl cellulose (CMC), carboxyethyl cellulose, chitin, carboxymethyl chitin, hyaluronic acid, alginate, propylene glycol alginate, carboxymethyl chitosan, pectin, carboxymethyl dextran, heparin, heparin sulfate, chondroitin sulfate and polyuronic acids including polymannuronic acid, polyglucuronic acid and polyguluronic acid.

59. The composition of claim 57, wherein the molecular weight of the CPS is between 100 kd and 10,000 kd.

60. The composition of claim 57, wherein the molecular weight of the PE is between about 4 kd and about 8000 kd.

61. The composition of claim 57, wherein the CPS is CMC.

62. The composition of claim 57, wherein the PE is polyethylene oxide (PEO).

63. The composition of claim 57, wherein the proportion of total solids content of the CPS is from 10 % to 95 % by weight, and the proportion of the PE is from 5 % to 90 % by weight.

64. The composition of claim 57, wherein the degree of substitution of the CPS is from greater than about 0 up to and including about 3.

65. The composition of claim 57 further comprising a drug.

66. The composition of claim 65, wherein said drug is selected from the group consisting of antibiotics, anti-inflammatory agents, hormones, chemotactic factors, peptides and proteins containing an RGD motif, analgesics, and anesthetics.

67. The composition of claim 57, further comprising multiple layers of membranes of CPS and PE.

68. The composition of claim 67 which has at least one property of being bioadhesive, resorbable or flexible, and wherein the property is adjusted by selecting at least one member from the group consisting of: (1) the molecular weight of the CPS in the range of about 100 kd and about 10,000 kd, (2) the molecular weight of the PE in the range of about 5 kd and about 8000 kd, (3) the degree of substitution of the CPS in the range of greater than about 0 and up to and including about 3, (4) the proportion of the CPS and the PE, wherein the proportion of the CPS in from about 10 % to about 95 % by weight, and the proportion of the PE is in the range of about 5 % to about 90 % by weight and (5) the membrane pH below between about 2.5 and about 4.5.

69. The composition of claim 57, further comprising a plasticizer.

70. The composition of claim 69, wherein the plasticizer is selected from the group consisting of glycerol, ethanolamines, ethylene glycol, 1,2,6-hexanetriol, monoacetin, diacetin, triacetin, 1,5-pentanediol, PEG, propylene glycol, and trimethylol propane.

71. The composition of claim 70, wherein the concentration of said plasticizer is in the range of greater than about 0 % to about 30 % by weight.

72. The composition of claim 70, wherein the plasticizer is glycerol in a concentration in the range of about 2 % to 30 % by weight.

73. The composition of claim 57, wherein the ratio of carbon atoms to oxygen atoms on the surface is between about 2 to about 4.

74. The composition of claim 57, wherein PEO is on the surface of said composition.

75. The composition of claim 57, wherein the C1s envelop comprises C-O bonds of greater than about 20% to about 100%.

76. The composition of claim 57, wherein the C1s envelop comprises C-O bonds of between about 25% to about 100 %.

77. The composition of claim 57, wherein the C1s envelop comprises C-O bonds of about 42%.

78. The composition of claim 57, wherein the O1s envelop comprises O-C bonds in the range of greater than about 73 % to about 100 %.

79. The composition of claim 57, wherein the O1s envelop comprises O-C bonds in the range of about 82% to about 100 %.

80. The composition of claim 57, wherein the adherence of platelets to the surface of said composition is in the range of about 0 platelets per 25,000 μm^2 to about 65 per 25,000 μm^2.

81. The composition of claim 57, wherein the adherence of platelets to the surface of said composition is in the range of about 0 platelets per 25,000 μm^2 to about 25 per 25,000 μm^2.

82. The composition of claim 57, wherein the adherence of platelets to the surface of said composition is in the range of about 0 platelets per 25,000 μm^2 to about 3 per 25,000 μm^2.

83. The composition of claim 57, wherein the plasma recalcification time is between about 6 minutes to about 20 minutes.

84. The composition of claim 57, wherein the plasma recalcification time is between about 13 minutes to about 18 minutes.

85. The composition of claim 57, wherein the plasma recalcification time is about 15 minutes.

86. A method of manufacturing a composition comprising of the steps of:

(a) preparing an aqueous solution of a CPS having a molecular weight in the range of

about 100 kd to about 10,000 kd; and wherein the degree of substitution of the CPS is in the range of greater than about 0 to 3.0;

(b) preparing an aqueous solution of a PE having a molecular weight in the range of

about 5 kd to about 8,000 kd;

(c) mixing said solution of said CPS and said solution of said PE together to form a

mixed solution of said CPS and said PE, and wherein the ratio of said CPS to said PE is in the range of about 1:9 to about 19:1;

(d) adjusting the pH of said mixed solution to a pH in the range of between about 2.5 and about 4.5; and

(e) drying said composition.

87. The method of claim 86, wherein the CPS is CMC and the PE is PEO.

88. The method of claim 86, further comprising the step of: increasing the pH of the dried composition.

89. The method of claim 86, wherein the the pH of the composition is increased to about 6.0.

90. The method of claim 89, wherein the step of increasing the pH comprises using a phosphate buffer, phosphate buffered saline or ammonia.

91. A method for reducing adhesion formation, comprising the steps of:

(a) accessing a surgical site; and

(b) delivering to said site, the gel of claim 1.

92. The method of claim 91, wherein the surgical procedure is selected from the group consisting of orthopedic, ophthalmic, gastrointestinal, abdominal, thoracic, cranial, otorhinolaryngological, cardiovascular, gynecological, arthroscopic, urological, dermal, subdermal, plastic and musculoskeletal.

93. The method of claim 91, further comprising the step of placing a dried composition of a CPS and a PE over said gel.

94. The gel of claim 1, wherein said multivalent cation is a polycation selected from the group consisting of polyaminoacids including polylysine and polyarginine, chitosan, basic proteins and basic peptides.

95. ~~94.~~ The method of claim 30, wherein said multivalent cation is a polycation selected from the group consisting of polyaminoacids including polylysine and polyarginine, chitosan, basic proteins and basic peptides.